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(54) Title: IMPLANTABLE POLYMERIC DEVICE FOR SUSTAINED RELEASE OF BUPRENORPHINE

(57) Abstract: The present invention provides compositions, methods, and kits for treatment of opiate addiction and pain. The invention provides a biocompatible nonerodible polymeric device which releases buprenorphine continuously with generally linear release kinetics for extended periods of time. Buprenorphine is released through pores that open to the surface of the polymeric matrix in which it is encapsulated. The device may be administered subcutaneously to an individual in need of continuous treatment with buprenorphine.



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IMPLANTABLE POLYMERIC DEVICE FOR SUSTAINED RELEASE OF BUPRENORPHINE

TECHNICAL FIELD

[0001] The invention provides a nonbioerodible, polymeric device for subcutaneous implantation and sustained release of buprenorphine for treatment of opiate addiction or pain.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made in part during work supported by a grant from the National Institute of Mental Health (1R43 MH60037-01). The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Buprenorphine, a semi-synthetic opiate classified as a “partial agonist” behaves very much like classical mu agonists such as morphine, exerting an analgesic effect through high affinity binding to mu subclass opiate receptors in the central nervous system.

[0004] Buprenorphine has been used as an analgesic for treatment of moderate to severe pain in postoperative cancer patients. Therapeutic doses administered by intravenous and intramuscular routes range from 0.3 to 0.6 mg. Buprenorphine produces effects similar to morphine but is 25-40 times more potent and has a large therapeutic index. Buprenorphine stimulates the mu opiate receptors in the brain and produces effects associated with other mu agonists such as morphine. Such effects include analgesia, euphoria, sedation, and respiratory depression. For this reason, oral buprenorphine formulations have the potential for misuse (*i.e.*, diversion for recreational, rather than therapeutic, purposes), making them unsuitable for use as a take-home medication.

[0005] Many patients with chronic pain require long-term continuous dosing with opiate analgesics. Effective treatment often necessitates the ingestion of multiple tablets per day. Compliance with this dosing scheme is often poor. Further, enteral drug delivery is poorly tolerated or prohibited in patients with particular indications, such as some

patients with cancer-related pain in whom continuous drug delivery is a necessity. However, continuous parenteral delivery of opiate analgesics is expensive, cumbersome, and dependent upon the availability of refrigeration, catheters, pumps, and trained personnel. Further, concerns over drug diversion for illicit use often limits availability of opiate analgesics. An oral tablet containing a combination of buprenorphine and naloxone, an opiate receptor antagonist, has been developed to address this issue (see, *e.g.*, U.S. Pat. No. 4,935,428). If an opiate addict attempts to abuse the combination tablet by dissolving it and injecting it intravenously, unpleasant withdrawal symptoms brought on by the naloxone component will result. However, opiate antagonists such as naloxone may reduce the analgesic effectiveness of buprenorphine to those who are using it therapeutically for pain relief and such antagonists may cause undesirable side effects. Thus, there is a need for an improved buprenorphine formulation which is administrable to those in need of analgesia but which provides a lower potential for abuse.

[0006] Buprenorphine has also been studied as a treatment for addiction to heroin and other opiates. Opiate addiction is a major societal problem throughout the world. The general treatment program for such addiction includes incorporation of a drug substitute, *e.g.*, methadone, into an oral formulation for administration to the drug addict. Typically, such drug substitutes function by binding to receptors specific for the drug of abuse. The effectiveness of such treatment depends largely upon adherence to an established treatment schedule. Often, poor compliance with dosing regimens complicates treatment. Further, the cost of such therapy is significant, a large portion of the cost relating to frequent clinic visits and the monitoring of urine tests to assure compliance with drug dosing, as well as pharmacy charges relating to dispensing of methadone. Another problem with oral dosage forms such as powders or tablets is that they can be dissolved in water and concentrated to provide a solution which may be injected by the addict in lieu of the drug of abuse. A means for long-term continuous administration of a drug suitable for treatment of opiate dependency in a form that is not subject to potential abuse, would significantly reduce the compliance problems encountered in drug addiction treatment programs.

[0007] Buprenorphine's unique effects and pharmacology make it a clinically attractive treatment option for opiate dependency. For example, buprenorphine produces less euphoria than morphine and heroin. When compared with other opiates, it also causes a significantly lower degree of sedation. Further, direct dependence studies have shown little physical dependence upon withdrawal of the drug.

[0008] There is a need for a buprenorphine formulation, suitable for long-term, continuous administration, that will improve compliance for both pain relief and drug dependency treatment regimens. There is also a need for a buprenorphine formulation that will reduce abuse potential, and in which the addition of an antagonist such as naloxone will not be necessary.

BRIEF SUMMARY OF THE INVENTION

[0009] The invention provides compositions (*i.e.*, implantable polymeric devices), methods, and kits for treatment of opiate addiction and pain.

[0010] In one aspect the invention provides an implantable device for treating opiate addiction, comprising buprenorphine and a biocompatible, nonerodible polymeric matrix, wherein said buprenorphine is encapsulated within said matrix, and wherein when said implantable device is implanted subcutaneously in a mammal, said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a rate that results in a steady state plasma buprenorphine level of at least about 0.1 ng/ml, typically in the range of about 0.1 to about 70 ng/ml. In some embodiments, the steady state plasma buprenorphine level is about 1 to about 10 ng/ml. In other embodiments, the steady state plasma buprenorphine level is about 1 to about 6 ng/ml. In some embodiments, the polymeric matrix comprises ethylene vinyl acetate copolymer (EVA). In some embodiments wherein the implantable device comprises EVA, the vinyl acetate content is about 33% by weight. The implantable devices generally comprise about 10% to about 85%, often about 50% to about 75% buprenorphine. In one embodiment, the implantable device comprises about 50% buprenorphine. In another embodiment, the implantable device comprises about 75% buprenorphine. In various embodiments, the sustained period of time for buprenorphine release is from about 3 months to about 1 year, or longer, *e.g.*, at least about 3, 6, 9, or 12 months. In some embodiments, the implantable device for treatment of opiate addiction is produced by an extrusion process. In one embodiment, extruded devices comprise dimensions of about 2.4 mm in diameter and about 2.6 cm in length. In other embodiments, extruded devices comprise dimensions of about 2 to about 3 mm in diameter and about 2 to about 3 cm in length. In further embodiments, extruded devices comprises dimensions of about 0.5 to about 7 mm in diameter and about 0.5 to about 10 cm in length. In some embodiments in

which extruded devices comprise dimensions of about 2.4 mm in diameter and about 2.6 cm in length, the devices each release about 1 mg buprenorphine per day *in vitro*.

[0011] In another aspect, the invention provides an implantable device for treating pain, comprising buprenorphine and a biocompatible, nonerodible polymeric matrix, wherein said buprenorphine is encapsulated within said matrix, and wherein when said implantable device is subcutaneously implanted in a mammal, said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a steady state rate of at least about 0.1 mg per day, generally in the range of about 0.1 to about 5 mg per day. In some embodiments, the steady state rate of buprenorphine release is about 0.3 mg per day. In some embodiments, the polymeric matrix comprises EVA. In some embodiments wherein the implantable device comprises EVA, the vinyl acetate content is about 33% by weight. The implantable devices generally comprise about 10% to about 85%, often about 50% to about 75% buprenorphine. In one embodiment, the implantable device comprises about 50% buprenorphine. In another embodiment, the implantable device comprises about 75% buprenorphine and about 25% EVA. In various embodiments, the sustained period of time for buprenorphine release is from about 3 months to about 1 year, or longer, *e.g.*, at least about 3, 6, 9, or 12 months. In some embodiments, the implantable device for treatment of pain is produced by an extrusion process. In one embodiment, extruded devices comprise dimensions of about 2.4 mm in diameter and about 2.6 cm in length. In other embodiments, extruded devices comprise dimensions of about 2 to about 3 mm in diameter and about 2 to about 3 cm in length. In further embodiments, extruded devices comprises dimensions of about 0.5 to about 7 mm in diameter and about 0.5 to about 10 cm in length. In some embodiments in which extruded devices comprise dimensions of about 2.4 mm in diameter and about 2.6 cm in length, the devices each release about 1 mg buprenorphine per day *in vitro*.

[0012] In one aspect, the invention provides a method for treatment of opiate addiction, comprising administering at least one implantable device for treatment of opiate addiction, as described above, subcutaneously, wherein each of said at least one implantable devices comprises buprenorphine encapsulated within a biocompatible, nonerodible polymeric matrix, wherein said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a rate that results in a steady state plasma buprenorphine level of at least about 0.1 ng/ml, generally about 0.1 to about 70 ng/ml. In some embodiments, the steady state plasma level

of buprenorphine is about 1 to about 10 ng/ml. In other embodiments, the steady state plasma level of buprenorphine is about 1 to about 6 ng/ml. In one embodiment, the method includes a multiplicity of individual implantable devices, wherein the combination of the implantable devices continuously releases buprenorphine *in vivo* over a sustained period of time at a steady state rate that results in a plasma buprenorphine level of about 0.1 to about 70, about 1 to about 10, or about 1 to about 6 ng/ml. In some embodiments, the polymeric matrix comprises EVA. In one embodiment, implantable devices comprise about 75% buprenorphine and about 25% EVA. In another embodiment, implantable devices comprise about 50% buprenorphine. In some embodiments wherein implantable devices comprise EVA, the vinyl acetate content is about 33% by weight. In various embodiments, the sustained period of time for buprenorphine release is from about 3 months to about 1 year, or longer, *e.g.*, at least about 3, 6, 9, or 12 months. In some embodiments, implantable devices for treatment of opiate addiction are produced by an extrusion process. In one embodiment, extruded devices comprise dimensions of about 2.4 mm in diameter and about 2.6 cm in length. In other embodiments, extruded devices comprises dimensions of about 2 to about 3 mm in diameter and about 2 to about 3 cm in length. In further embodiments, extruded devices comprise dimensions of about 0.5 to about 7 mm in diameter and about 0.5 to about 10 cm in length. In some embodiments in which extruded devices comprises dimensions of about 2.4 mm in diameter and about 2.6 cm in length, the devices each release about 1 mg buprenorphine per day *in vitro*. In methods of the invention, the implantable devices are administered by subcutaneous implantation. In various embodiments, the devices are subcutaneously implanted at a site selected from the group consisting of the upper arm, the back, and the abdomen.

[0013] In another aspect, the invention provides a method for treatment of pain, comprising administering at least one implantable device for treatment of pain, as described above, subcutaneously, wherein each of said at least one implantable devices comprises buprenorphine encapsulated within a biocompatible, nonerodible polymeric matrix, wherein said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a steady state rate of at least about 0.1 mg per day, often in the range of about 0.1 to about 5 or about 0.2 to about 1 mg per day. In some embodiments, the steady state rate of buprenorphine release is about 0.3 mg per day. In one embodiment, the method includes a multiplicity of individual implantable devices, wherein the combination of the implantable devices continuously releases

buprenorphine *in vivo* over a sustained period of time at a steady state rate of about 0.1 to about 5, about 0.2 to about 1, or about 0.3 mg per day. In some embodiments, the polymeric matrix comprises EVA. In one embodiment, implantable devices comprise about 75% buprenorphine and about 25% EVA. In another embodiment, implantable devices comprise about 50% buprenorphine. In some embodiments wherein implantable devices comprise EVA, the vinyl acetate content is about 33% by weight. In various embodiments, the sustained period of time for buprenorphine release is from about 3 months to about 1 year, or longer, *e.g.*, at least about 3, 6, 9, or 12 months. In some embodiments, implantable devices for treatment of pain are produced by an extrusion process. In methods of the invention, the implantable devices are administered by subcutaneous implantation. In various embodiments, the devices are subcutaneously implanted at a site selected from the group consisting of the upper arm, the back, and the abdomen.

[0014] In one aspect, the invention provides a kit for use in treatment of opiate addiction, comprising at least one implantable device for treatment of opiate addiction, as described above, comprising buprenorphine encapsulated within a biocompatible, nonerodible polymeric matrix, wherein when said at least one implantable device is implanted subcutaneously in a mammal, said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a rate that results in a steady state plasma level of about 0.1 to about 70 ng/ml, and instructions for use. In some embodiments, the steady state plasma level is about 1 to about 10 ng/ml. In other embodiments, the steady state plasma level is about 1 to about 6 ng/ml. In some embodiments, kits include a multiplicity of individual implantable devices, wherein when said multiplicity of devices is implanted subcutaneously in a mammal, the combination of the implantable devices continuously releases buprenorphine *in vivo* over a sustained period of time at a rate that results in a steady state plasma level of about 0.1 to about 70, often about 1 to about 10, more often about 1 to about 6 ng/ml. In one embodiment, each of the individual implantable devices releases buprenorphine at a rate of about 1 mg per day *in vitro*. In some embodiments, the polymeric matrix comprises EVA. In various embodiments, implantable devices comprise about 10 to about 85% buprenorphine. In some embodiments wherein implantable devices comprise EVA, the vinyl acetate content is about 33% by weight.

[0015] In another aspect, the invention provides a kit for use in treatment of pain, comprising at least one implantable device for treatment of pain, as described above, comprising buprenorphine encapsulated within a biocompatible, nonerodible polymeric matrix, wherein when said at least one implantable device is implanted subcutaneously in a mammal, said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface at a steady state rate of at least about 0.1 mg per day, generally in the range of about 0.1 to about 5 or about 0.2 to about 1 mg per day, and instructions for use. In one embodiment, the steady state rate of buprenorphine release is about 0.3 mg per day. In some embodiments, kits include a multiplicity of individual implantable devices, wherein when said multiplicity of devices is implanted subcutaneously in a mammal, the combination of the implantable devices continuously releases buprenorphine *in vivo* over a sustained period of time at a rate of about 0.1 to about 5, 0.2 to about 1, or about 0.3 mg per day. In some embodiments, the polymeric matrix comprises EVA. In various embodiments, implantable devices comprise about 10 to about 85% buprenorphine. In some embodiments wherein implantable devices comprise EVA, the vinyl acetate content is about 33% by weight.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] **Fig. 1** depicts *in vitro* release of buprenorphine over time from a single irradiated extruded rod containing 75% buprenorphine HCl and 25% EVA (33% vinyl acetate). Fig. 1A shows the average cumulative release of buprenorphine HCl in 0.5% SDS at 37° C. Fig. 1B shows the average daily release of buprenorphine HCl in 0.5% SDS at 37° C.

[0017] **Fig. 2** depicts *in vivo* release of buprenorphine from devices of the invention implanted subcutaneously in dogs for 84 days. Two devices, each with dimensions of about 2.6 cm in length and about 2 mm in diameter, and containing 75% buprenorphine HCl and 25% EVA (33% vinyl acetate), were implanted in each dog.

[0018] **Fig. 3** depicts *in vivo* release of buprenorphine when 8, 16, or 24 implantable devices were implanted subcutaneously in dogs for 8 months.

[0019] **Fig. 4** depicts the steady state plasma concentration of buprenorphine achieved when 2, 8, 16, or 24 implantable devices were implanted subcutaneously in dogs.

DETAILED DESCRIPTION OF THE INVENTION

[0020] The invention provides a biocompatible, nonerodible polymeric device, which permits controlled, sustained release of buprenorphine over extended periods of time when implanted subcutaneously in an individual in need of treatment.

[0021] Continuous release of a compound *in vivo* over an extended duration may be achieved via implantation of a device containing the compound encapsulated in a nonerodible polymeric matrix. Examples of implantable, nonerodible polymeric devices for continuous drug release are described in, *e.g.*, U.S. Pat. Nos. 4,883,666, 5,114,719, and 5,601,835. Implantable devices improve compliance with drug dosing regimens, due to continuous release of the drug from the polymeric matrix, and reduce abuse potential since such devices are not as subject to diversion as other formulations, such as, for example, oral dosage forms.

[0022] Implantation of the device and extended release of buprenorphine limits or prevents diversion of the drug to nonintended users and improves compliance with dosing regimens, eliminating the need for repeated injections or ingestion of pills or tablets. An implantable, sustained-release device according to the present invention also permits achievement of more constant blood levels of buprenorphine than injectable or oral dosage forms, thereby minimizing side effects.

[0023] Previous vehicles for long term delivery of buprenorphine have included biodegradable polymers (U.S. Pat. No. 5,486,362). However, in contrast to the present invention, such polymers do not release compounds at linear rates for extended time periods of several months or longer, because channels form in the matrix as it erodes, resulting in increased release rates over time. The present invention includes a biocompatible, nonerodible polymer that exhibits generally linear release kinetics for buprenorphine *in vivo*, after an initial burst.

Implantable Polymeric Devices for Treatment of Opiate Addiction or Pain

[0024] The invention includes implantable devices for treatment of opiate addiction or pain, including buprenorphine encapsulated in a polymeric, nonerodible matrix. As used herein, "buprenorphine" refers to buprenorphine free base and pharmaceutically acceptable salts thereof, such as buprenorphine HCl, and norbuprenorphine. Incorporation of buprenorphine into the polymeric matrix causes the formation of a series of interconnecting channels and pores that are accessible to the surface for release of the drug. Where

appropriate, a coating that is impermeable to the drug is placed over at least a portion of the device to further regulate the rate of release. When implanted subcutaneously, devices of the invention continuously release buprenorphine for an extended period of time with a pseudo or near zero order release rate. After an initial burst following implantation, release rates are typically within about 10-20% of the steady state average. In some embodiments, the initial burst of buprenorphine released *in vivo* after implantation is reduced or minimized by prewashing the implantable devices before implantation to remove surface buprenorphine. Prewashing may be performed in any solution in which buprenorphine is soluble, for example 30 minutes in ethanol or normal saline.

[0025] As used herein, “nonerodible matrix” refers to a polymeric carrier that is sufficiently resistant to chemical and/or physical destruction by the environment of use such that the matrix remains essentially intact throughout the release period. The polymer is generally hydrophobic so that it retains its integrity for a suitable period of time when placed in an aqueous environment, such as the body of a mammal, and stable enough to be stored for an extended period before use. The ideal polymer must also be strong, yet flexible enough so that it does not crumble or fragment during use. Nonerodible matrices remain intact *in vivo* for extended periods of time, typically months or years. Drug molecules encapsulated in the matrix are released over time via diffusion through channels and pores in a sustained and predictable manner. The release rate can be altered by modifying the percent drug loading, porosity of the matrix, structure of the implantable device, or hydrophobicity of the matrix, or by adding a hydrophobic coating to the exterior of the implantable device.

[0026] Typically, ethylene vinyl acetate copolymer (EVA) is used as the polymeric matrix, but other nonerodible materials may be used. Examples of other suitable materials include silicone, hydrogels such as crosslinked poly(vinyl alcohol) and poly(hydroxy ethylmethacrylate), acyl substituted cellulose acetates and alkyl derivatives thereof, partially and completely hydrolyzed alkylene-vinyl acetate copolymers, unplasticized polyvinyl chloride, crosslinked homo- and copolymers of polyvinyl acetate, crosslinked polyesters of acrylic acid and/or methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride, polycarbonate, polyurethane, polyamide, polysulphones, styrene acrylonitrile copolymers, crosslinked poly(ethylene oxide), poly(alkylenes), poly(vinyl imidazole), poly(esters), poly(ethylene terephthalate), polyphosphazenes, and chlorosulphonated polyolefines, and combinations thereof.

[0027] Implantable devices of the invention are typically formulated with buprenorphine loading of about 10% to about 85%. Often, the devices include about 50% to about 75% buprenorphine. Devices are sometimes formulated as compositions including about 75% buprenorphine and about 25% EVA (33% vinyl acetate). In various embodiments, devices include any of at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, or 85% buprenorphine. Devices may be produced using an extrusion process, wherein ground EVA is blended with buprenorphine, melted, and extruded into rod-shaped structures. Rods are cut into individual implantable devices of the desired length, packaged, and sterilized prior to use. Other methods for encapsulating therapeutic compounds in implantable polymeric, nonerodible matrices are well known to those of skill in the art. Such methods include, for example, solvent casting (see, *e.g.*, U.S. Pat. Nos. 4,883,666, 5,114,719, and 5,601,835). A skilled artisan would be able to readily determine an appropriate method of preparing such an implantable device, depending on the shape, size, drug loading, and release kinetics desired for a particular type of patient or clinical indication.

[0028] Devices of the invention are suitable for sustained release of buprenorphine for treatment of opiate addiction or pain. As used herein, "sustained release" refers to the release of buprenorphine such that the blood concentration remains within the therapeutic range but below toxic levels for an extended duration. Devices of the invention generally exhibit near zero-order pharmacokinetics *in vivo*, similar to kinetics achieved with an IV drip, but without the need for external medical equipment and personnel associated with intravenous methods. Generally, after implantation, the devices release therapeutically effective amounts of buprenorphine for periods of several months up to one year or longer. Often, the duration of implantation, with continuous release of buprenorphine, is from about 3 months to about 2 years, about 3 months to about 1 year, about 3 months to about 9 months, or about 3 months to about 6 months. In various embodiments, therapeutically effective amounts of buprenorphine are released for at least about 3, 6, 9, 12, 15, 18, 21, or 24 months.

[0029] Multiple implantable devices may be used, or the size and shape of the devices may be modified, to achieve a desired overall dosage. Implantable devices are often about 0.5 to about 10, more often about 1.5 to about 5, most often about 2 to about 3 cm in length, and are often about 0.5 to about 7, more often about 1.5 to about 5, most often about 2 to about 3 mm in diameter. The release rate of implantable devices may also be

modified by changing the vinyl acetate content in the EVA polymer matrix. The vinyl acetate content is often about 2 to about 40, more often about 10 to about 35, most often about 30 to about 35 % by weight.

[0030] The desired dosage rate will depend upon factors such as the underlying condition for which buprenorphine is being administered, and the physiology of a particular patient, but will be readily ascertainable to physicians. For treatment of opiate addiction, buprenorphine is desirably released at a rate that maintains plasma levels of the drug at a therapeutically effective level. Often, a desirable plasma level of buprenorphine for treatment of opiate addiction is in the range of about 0.1 to about 70 ng/ml, more often about 1 to about 10 ng/ml, most often about 1 to about 6 ng/ml. In various embodiments for treatment of opiate addiction, buprenorphine is released from one or more devices *in vivo* at a rate that results in a plasma level of at least about 0.1, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 15, 25, 50, or 70 ng/ml. For treatment of pain, a therapeutically effective amount of buprenorphine is typically about 0.1 to about 5 mg/day, sometimes about 0.2 to about 1 mg/day, often about 0.3 mg/day, but may be modified depending upon the nature of the pain condition being treated and the particular patient involved. In various embodiments for treatment of pain, one or more devices are used that are capable of releasing at least about 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, or 5 mg/day *in vivo* or *in vitro*. As used herein, “therapeutically effective amount” or “therapeutically effective level” refers to the amount of buprenorphine that will render a desired therapeutic outcome (*i.e.*, reduction of self-administration of nonprescribed drugs, or analgesic relief of pain).

Methods of the Invention

[0031] The invention provides methods for treatment of opiate addiction and pain. Methods of the invention include subcutaneous administration of one or more polymeric implantable devices which include buprenorphine encapsulated within a biocompatible, nonerodible polymeric matrix such as EVA, and release of buprenorphine in a controlled manner over an extended period of time through multiple pores that open to the surface of the implantable device(s). Often, implantable devices are produced via an extrusion process, as described above.

[0032] Implantable devices are administered by subcutaneous implantation to an individual in need of treatment. As used herein, “individual” refers to a mammal, typically a human in need of treatment for opiate addiction or pain. Generally, implantable devices

are administered by subcutaneous implantation at sites on the upper arm, back, or abdomen of an individual. Other suitable sites for administration may be readily determined by a medical professional. Multiple implantable devices may be administered to achieve a desired dosage for treatment.

[0033] Typically, in a method for treatment of opiate addiction, an implantable device or devices are administered that will release buprenorphine at a rate that will maintain a therapeutically effective plasma level for an extended period of time of at least about 3 months. When multiple devices are administered, the combination of the devices releases buprenorphine at a rate that will achieve a therapeutically effective plasma level. A therapeutically effective plasma level for treatment of opiate addiction is often about 0.1 to about 70 ng/ml, more often about 1 to about 10 ng/ml, most often about 1 to about 6 ng/ml. Often, sustained release at this dosage rate occurs for about 3 months to about 1 year or longer (*e.g.*, at least about 3, 6, 9, or 12 months). As used herein, "opiate addiction" or "opiate dependency" refers to dependence by an individual on an opiate substance which is treatable by administration of a substitute substance, such as methadone or buprenorphine. It is anticipated that the implantable devices of the invention will alleviate compliance and diversion problems encountered with traditional methadone treatment regimens, as described above.

[0034] Further, in accordance with the present invention, a method of alleviating pain is provided which includes subcutaneous administration of an implantable nonerodible polymeric device which releases an analgesically effective amount of buprenorphine in a controlled manner for an extended period of time, *i.e.* about 3 months to about 1 year (*e.g.*, at least about 3, 6, 9, or 12 months) or longer, to an individual exhibiting pain. An implantable device is chosen for a particular patient or pain indication such that an analgesically effective amount of buprenorphine will be continuously released. As used herein, the term "analgesically effective amount" refers to an amount of buprenorphine sufficient to achieve a reduction in or elimination of pain in a mammalian subject without loss of consciousness. The effectiveness of analgesia provided by an analgesic substance can be assessed by methods that are well known to those skilled in the art. For example, U.S. Pat. No. 6,228,863 describes assessment by direct measurement in human patients or by the use of one or more surrogate measures. Direct measurement may include scoring an analgesic questionnaire reported by patients at serial times following administration of the analgesic substance. Summary measures of analgesia include the sum of pain intensity

difference (SPID) and total pain relief (TOTPAR). Surrogate measures for determining analgesic effectiveness in human subjects include assessment of sedation, respiratory rate and/or pupil size, and visual analogue scale for drug effect. Effectiveness of analgesia may also be assessed using animal models. For example, U.S. Pat. No. 4,599,342 describes a mouse hot plate test and a phenylquinone writhing test model for assessing the extent of analgesia.

[0035] The method of alleviating pain according to the present invention is applicable to the treatment of all pain conditions which require continuous administration of an analgesic substance, *e.g.*, postoperative pain, cancer pain, arthritic pain, lumbosacral pain, musculoskeletal pain, neuropathic pain, etc. This list, however, should not be interpreted as exhaustive. It is contemplated that the method of the invention will improve compliance with dosing regimens for therapeutic pain relief, while reducing the amount of opiate substances that are available for diversion to nonintended users, *i.e.*, drug addicts. Long term continuous release should also reduce or eliminate the peaks and troughs of blood analgesic concentration associated with other formulations such as oral dosage forms. Typically, the steady state release rate of buprenorphine used for pain relief methods is from about 0.1 to about 5, sometimes about 0.2 to about 1, often about 0.3 mg per day.

[0036] In any of the above methods, the length of time during which buprenorphine is continuously administered may be extended by reimplanting additional implantable devices in an individual receiving treatment before or after plasma levels of buprenorphine begin to decline, to maintain buprenorphine at the desired steady state level.

Kits

[0037] The invention also provides kits for use in treatment of opiate addiction or pain. The kits include at least one implantable, nonerodible device of the type herein described, capable of delivering long-term therapeutic levels of buprenorphine, in suitable packaging, along with instructions providing information to the user and/or health care provider regarding subcutaneous implantation and use of the system for treating drug dependence or pain. Kits may also include literature discussing performance of the implantable devices of the invention. Kits include a delivery system, *i.e.*, one or a multiplicity of implantable devices, capable of providing sustained release of therapeutic levels of buprenorphine for at least about 3 months. Kits for treatment of opiate addiction

typically contain a polymeric, nonerodible delivery system capable of continuously releasing buprenorphine at a rate sufficient to achieve a therapeutically effective plasma level of about 0.1 to about 70, about 1 to about 10, or about 1 to about 6 ng/ml for at least about 3 months. Kits for treatment of pain typically contain a delivery system capable of releasing a total continuous analgesically effective dosage of about 0.1 to about 5, about 0.2 to about 1, or about 0.3 mg buprenorphine per day for at least about 3 months. In kits of the invention, implantable devices may be preloaded into devices such as, for example, syringes or trocars, capable of administering them by subcutaneous implantation into patients.

EXAMPLES

The following examples are intended to illustrate but not limit the invention.

Example 1 - Materials and Methods

Materials

[0038] The following materials were used:

- Buprenorphine HCl, 99.3%, supplied by Macfarlan Smith Limited, Wheatfield Road, Edinburgh, EH 11 2QA
- Buprenorphine base, supplied by Diosynth B.V. Vlijtseweg 130, 7317 AK Apeldoorn, The Netherlands
- Buprenorphine HCl, supplied by Diosynth B.V. Vlijtseweg 130, 7317 AK Apeldoorn, The Netherlands
- Methanol-ChromAR, HPLC grade, supplied by Mallinckrodt, St. Louis, MO
- Acetonitrile, HPLC grade, supplied by Mallinckrodt, St. Louis, MO
- Sodium lauryl sulfate, 99%, supplied by Sigma Chemicals, St. Louis, MO
- EVA, 33% vinyl acetate, supplied by Equistar Chemicals, LP, Houston, TX
- Tower Plasti-Peel pouches, Catalog #30307PN, supplied by DRG Medical Packaging, Mundelein, IL

Preparation of Implantable Devices

[0039] Buprenorphine is available as a salt (HCl) and as a free base. The implantable device is intended to release drug over a 3-month period or longer, so preliminary studies were performed to select the form of buprenorphine suitable for sustained release. Buprenorphine was incorporated at 50% drug load in the copolymer, using the free base form and the HCl salt. Extruded rods were prepared and comparative *in vitro* evaluations were conducted to select the drug form, based on the results of these studies.

[0040] Implantable devices were prepared using an extrusion process. As a result of initial loading experiments with lactose, two sets of extrusion parameters were identified that produced implantable devices with a smooth exterior finish and homogeneous drug content. The extrusion parameters were as follows:

<u>Set 1</u>	Zone 1:	210°F
	Zone 2:	230°F
	Zone 3:	210°F
	Die:	214°F
	RPM:	67
	Die orifice:	2.18 mm

Set 1 parameters were used for the preparation of rods incorporating 50% buprenorphine free base and HCl salt.

<u>Set 2</u>	Zone 1:	210°F
	Zone 2:	230°F
	Zone 3:	230°F
	Die:	240°F
	RPM:	40
	Die orifice:	1.95 mm

Set 2 parameters were used for the preparation of rods incorporating 75% buprenorphine HCl salt, which were used for *in vitro* and *in vivo* studies as described below.

[0041] The ground copolymer and compound to be incorporated were used as received from the manufacturer. The extruded rods were cut into uniform lengths of 25 mm, packaged in polyester/Tyvek bags, heat sealed, and shipped to Steris/Isomedix (Libertyville, IL) for terminal sterilization by gamma irradiation.

HPLC Assays

[0042] HPLC analysis was used to determine the rate of *in vitro* release of buprenorphine from buprenorphine-containing implants. Chromatography was performed

using a Waters Novapak C-18 (150 mm x 3.9 mm, SN. E5003B) column and 0.05 M sodium acetate, pH 5 (Solution A) and a mixture of methanol/acetonitrile (2:1 v/v) (Solution B) as the mobile phase, at a ratio of 35%A and 65%B and a flow rate of 1 ml/min. The injection volume was 100 μ l. Detection was accomplished by means of a UV/VIS (Waters Model 490) detector at a wavelength of 285 nm. Instrument control and data acquisitions were facilitated using a Waters Millennium (V 2.15) software package. The external calibration was obtained using buprenorphine standard solutions prepared in 2:1 (v/v) acetonitrile:methanol.

[0043] The calibration curve for the buprenorphine standard over a concentration range of 2.5-500 μ g/ml indicated linearity, with r^2 values greater than 0.99.

LC/MS/MS Assay

[0044] An LC/MS/MS method was used to determine levels of buprenorphine released from the implants *in vivo*.

Buprenorphine

[0045] Dog plasma (0.500 ml) containing buprenorphine and a D4-buprenorphine internal standard was extracted with hexane/isoamyl alcohol. Following centrifugation, transfer of the organic layer and evaporation, the dried extract was derivatized with pentafluoropropionic anhydride (PFPA). After the reaction, the excess reagent was evaporated and an aliquot of the reconstituted extract was injected onto a SCIEX API III Plus LC-MS-MS apparatus in positive ion mode equipped with an HPLC column. Peak areas of the m/z 596 to 564 product ion of buprenorphine-PFP were measured against the m/z 600 to 568 product ion of the internal standard in MRM mode. Quantitation was performed using a weighted linear least squares regression analysis generated from spiked plasma calibration samples.

Norbuprenorphine

[0046] Dog plasma (0.500 ml) containing norbuprenorphine and a D3-norbuprenorphine internal standard was basified and extracted with ethyl acetate. Following evaporation, the dried extract was derivatized with acetic anhydride. After the

reaction, the excess reagent was evaporated and an aliquot of the reconstituted extract was injected onto a SCIEX API III-Plus LC-MS-MS apparatus equipped with an HPLC column. Peak areas of the m/z 586 to 498 product ion of the norbuprenorphine derivative was measured against the peak areas of the m/z 589 to 501 product ion of the internal standard. Quantitation was performed using the peak areas of the m/z 589 to 501 product ion of the internal standard. Quantitation was performed using a weighted linear least squares regression analysis generated from fortified plasma calibration samples.

Example 2 - In Vitro Characterization of Extruded Implantable Devices

[0047] Extruded rods prepared as described above were characterized for total drug load and for rate of drug release.

Assessment of Drug Loading

[0048] Extruded rods were accurately weighed, placed in tightly closed borosilicate glass jars containing 50 ml of methanol, and continuously stirred at room temperature. Sample aliquots were removed periodically and analyzed by HPLC. Initial experiments indicated that the incorporated compounds were completely extracted within 24 hr. Irradiated and nonirradiated rods were compared side by side.

[0049] Drug loading studies indicated that the physical mixtures were homogeneous and contained the estimated quantities of buprenorphine. Table 1 shows the recovery for the free base (FB) and HCl salt at 50% loading. Table 2 shows the recovery of buprenorphine HCl at 75% loading, and indicates that the average drug load before and after gamma radiation was >75%.

Table 1. Recovery of buprenorphine at 50% drug loading.

Drug	Sample 1 (% drug load)	Sample 2 (% drug load)	Average (% drug load)
Buprenorphine HCl	51.0	49.6	50.3
Buprenorphine FB	45.5	46.5	46.0

Table 2. Recovery of buprenorphine HCl at 75% drug loading.

Before Radiation (% drug load)	After Radiation (% drug load)
Average = 77.3	Average = 75.5
SD = +/- 4.2	SD = +/- 3.6

Assessment of Drug Release

[0050] Experiments were performed to determine the rate of buprenorphine released from the extruded rods. The medium for these studies was 0.5% sodium lauryl (dodecyl) sulfate (SDS). The preweighed rods were placed in 100 ml screw cap jars containing 50 ml of medium and placed on an orbital shaker. The orbital shaker was housed in an incubator maintained at 37°C. Sampling of the medium was performed by replacing the media periodically. The samples obtained were analyzed by HPLC.

[0051] Comparison of the *in vitro* release of buprenorphine base and salt form indicated that daily release for the HCl salt, after an initial burst, was closer than that of the free base to the desired range of about 1 mg/day (Figure 1). Thus, the HCl salt was selected for further studies.

Example 3 - *In Vivo* Evaluation of Drug Loaded Implantable Devices

[0052] Three female beagle dogs were administered two sterilized implantable devices each containing 75% buprenorphine HCl in EVA containing 33% vinyl acetate, as described above (2 mm diameter x 2.6 cm length rods). Implantable devices were administered by subcutaneous injection to the dorsal region of each dog using a trocar. Blood samples were withdrawn periodically over a period of 84 days and frozen. The

frozen samples were analyzed by LC/MS/MS for content of buprenorphine and norbuprenorphine (the major metabolite).

[0053] After an initial burst, the mean buprenorphine plasma levels were maintained around 0.75 - 1.0 ng/ml through day 84. The mean buprenorphine and norbuprenorphine levels were similar in all three dogs. The peak concentration of buprenorphine in the plasma ranged from 2.41 to 6.32 ng/ml. After the initial burst effect, a slow decrease in plasma concentration of buprenorphine was observed for all the dogs. On day 84, plasma concentration of buprenorphine ranged from 0.72 to 0.99 ng/ml. No signs of toxicity or irritation and/or inflammation at the sites of implantation were observed in any of the dogs. Further, no vascularization or minimal fibrous capsule formation were observed. The plasma concentration of buprenorphine over time for this experiment is shown in Fig. 2.

Example 4 - Long Term Delivery of Buprenorphine via an Implantable Delivery

System *in vivo*

[0054] *In vivo* release of buprenorphine from polymeric implantable devices was investigated in toxicology studies in beagle dogs over an eight month period of time. Four dosage groups were treated with 2, 8, 16, or 24 implantable devices (rod-shaped devices containing 25% buprenorphine HCl and 75% EVA with 33% vinyl acetate, as described in Example 3). Implantable devices were administered subcutaneously in the dorsal regions of dogs via trocar under sterile conditions. Blood samples were collected from the jugular veins at various times for 8 months post implantation. Plasma concentrations of buprenorphine were quantified by LC/MS/MS. Animals were monitored for complications including irritation, inflammation, or infection at the treatment site. Pharmacokinetic parameters observed for the different dosage groups are represented in Table 3.

TABLE 3
Pharmacokinetic Parameters Calculated from Plasma Concentrations

Number of Implants	Mean C_{\max}^a (ng/mL)	Mean t_{\max}^b (day)	Mean C_{ss}^c (ng/mL)	Half-Life to C_{ss} (weeks)	Number of Dogs, n
2	4.4	1	0.81 ± 0.1	0.7	3
8	21.6	1	3.2 ± 0.4	2	2
16	36.1	1	4.6 ± 0.5	2	2
24	74.6	1	9.3 ± 0.7	2	10

^aMaximum concentration of buprenorphine achieved in plasma

^bTime of maximum plasma concentration of buprenorphine

^cMean steady-state plasma concentration

[0055] After an initial burst, pharmacokinetics were linear and dose proportional with 2 and 8 implantable devices, and were saturable and nonlinear with 16 and 24 devices (Figure 3). Steady-state concentrations of 0.81 ± 0.1 and 3.2 ± 0.4 ng/ml were achieved within 3 weeks with 2 and 8 devices, respectively (Figure 4). Steady-state concentrations of 4.6 ± 0.5 and 9.3 ± 0.7 ng/ml were achieved within 8 weeks with 16 devices and 10 weeks with 24 devices, respectively. Upon reaching steady state, buprenorphine levels remained steady, with a concentration variability of about 10-20%, until 8 months post implantation, at which time the implantable devices were removed. Norbuprenorphine plasma concentrations remained below detectable levels. The additional time required to reach steady state with 16-24 implantable devices may be attributable to limited diffusion of the drug due to saturation of the space between the devices and blood capillaries, or due to saturation of capillary absorptive surface area.

[0056] No significant systemic or local (implantation site) adverse effects were observed in any of the dogs. Minor irritation at the treatment site was observed in three dogs. No adverse behavioral effects were observed other than lethargy on the first day after implantation for animals receiving the maximum dosage (*i.e.*, 24 devices). Upon removal of the devices after 8 months, no areas of necrosis or visible vascularization were observed in the tissue that had been surrounding the devices.

[0057] Although the foregoing invention has been described in some detail by way of illustration and examples for purposes of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications may be practiced without

departing from the spirit and scope of the invention. Therefore, the description should not be construed as limiting the scope of the invention, which is delineated by the appended claims.

[0058] All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety.

CLAIMS

We claim:

1. An implantable device for treating opiate addiction, comprising buprenorphine and a biocompatible, nonerodible polymeric matrix, wherein said buprenorphine is encapsulated within said matrix, and wherein when said implantable device is implanted subcutaneously in a mammal, said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a rate that results in a steady state plasma buprenorphine level of at least about 0.1 ng/ml.
2. An implantable device according to claim 1, wherein the polymeric matrix comprises ethylene vinyl acetate copolymer (EVA).
3. An implantable device according to claim 2, wherein said EVA comprises about 33% vinyl acetate.
4. An implantable device according to any preceding claim, comprising about 10 to about 85% buprenorphine.
5. An implantable device according to claim 4, comprising about 50% buprenorphine.
6. An implantable device according to claim 4, comprising about 75% buprenorphine.
7. An implantable device according to any preceding claim, wherein the implantable device is produced by an extrusion process.
8. An implantable device according to claim 7, comprising dimensions of about 2 to about 3 mm in diameter and about 2 to about 3 cm in length.

9. An implantable device according to claim 8, comprising dimensions of about 2.4 mm in diameter and about 2.6 cm in length.
10. An implantable device according to claim 9, wherein said implantable device releases about 1 mg buprenorphine per day *in vitro*.
11. An implantable device according to any preceding claim, wherein the sustained period of time is at least about 3 months.
12. An implantable device for treating pain, comprising buprenorphine and a biocompatible, nonerodible polymeric matrix,
wherein said buprenorphine is encapsulated within said matrix, and
wherein when said implantable device is subcutaneously implanted in a mammal, said buprenorphine is continuously released *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a steady state rate of at least about 0.1 mg per day.
13. An implantable device according to claim 12, wherein the polymeric matrix comprises EVA.
14. An implantable device according to claim 13, wherein said EVA comprises 33% vinyl acetate.
15. An implantable device according to any of claims 12 to 14, comprising about 10 to about 85% buprenorphine.
16. An implantable device according to claim 15, comprising about 50% buprenorphine.
17. An implantable device according to claim 15, comprising about 75% buprenorphine.

18. An implantable device according to any of claims 12 to 17, wherein the implantable device is produced by an extrusion process.

19. An implantable device according to claim 18, comprising dimensions of about 2 to about 3 mm in diameter and about 2 to about 3 cm in length.

20. An implantable device according to claim 19, comprising dimensions of about 2.4 mm in diameter and about 2.6 cm in length.

21. An implantable device according to claim 20, wherein said implantable device releases about 1 mg buprenorphine per day *in vitro*.

22. An implantable device according to any of claims 12 to 21, wherein the sustained period of time is at least about 3 months.

23. A method for treatment of opiate addiction, comprising administering at least one implantable device according to any of claims 1 to 11 subcutaneously, wherein said at least one implantable device releases buprenorphine *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a rate that results in a steady state plasma buprenorphine level of about 1 to about 10 ng/ml.

24. A method according to claim 23, wherein said at least one implantable device comprises a multiplicity of individual implantable devices, and wherein the combination of said implantable devices continuously releases buprenorphine *in vivo* over a sustained period of time at a rate that results in a steady state plasma buprenorphine level of about 1 to about 10 ng/ml.

25. A method according to claim 23 or 24, wherein each of said at least one implantable devices is subcutaneously implanted at a site selected from the group consisting of the upper arm, the back, and the abdomen.

26. A method for treatment of pain, comprising administering at least one implantable device according to any of claims 12 to 22 subcutaneously,

wherein said at least one implantable devices continuously releases buprenorphine *in vivo* over a sustained period of time through pores that open to the surface of said matrix at a steady state rate of about 0.1 to about 5 mg per day.

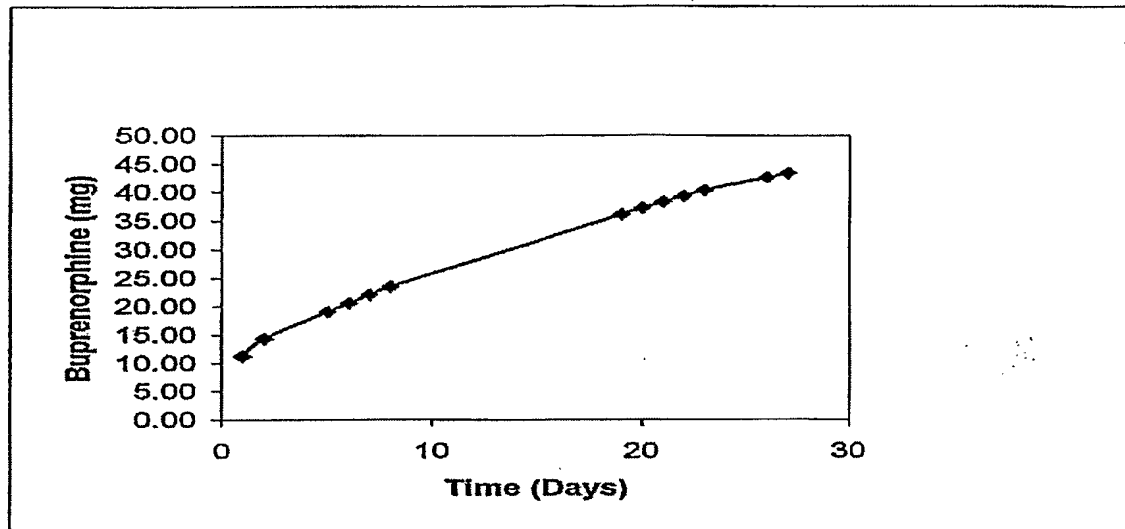
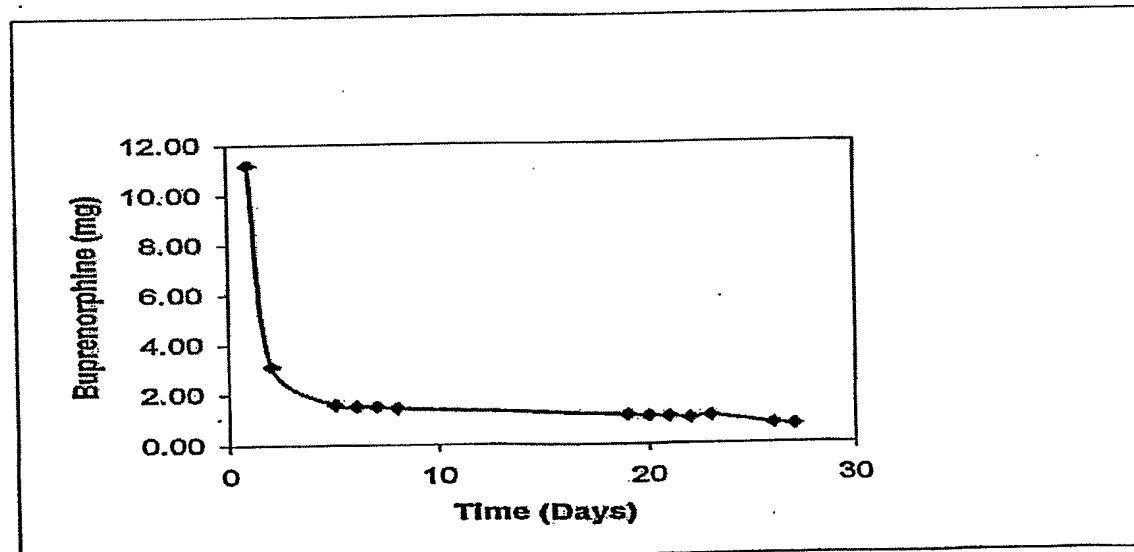
27. A method according to claim 26, wherein said at least one implantable device comprises a multiplicity of individual implantable devices, and wherein the combination of said implantable devices continuously releases buprenorphine *in vivo* over a sustained period of time at a steady state rate of about 0.1 to about 5 mg per day.

28. A method according to claim 26 or 27, wherein each of said at least one implantable devices is subcutaneously implanted at a site selected from the group consisting of the upper arm, the back, and the abdomen.

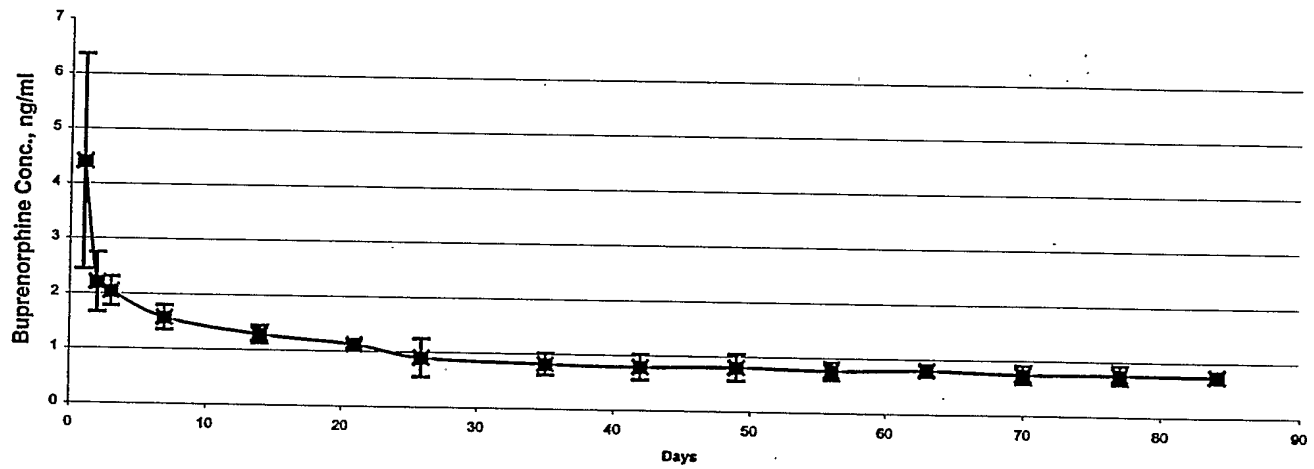
29. A kit for use in treatment of opiate addiction, comprising at least one implantable device according to any of claims 1 to 11, and instructions for use.

30. A kit for use in treatment of pain, comprising at least one implantable device according to any of claims 12 to 22, and instructions for use.

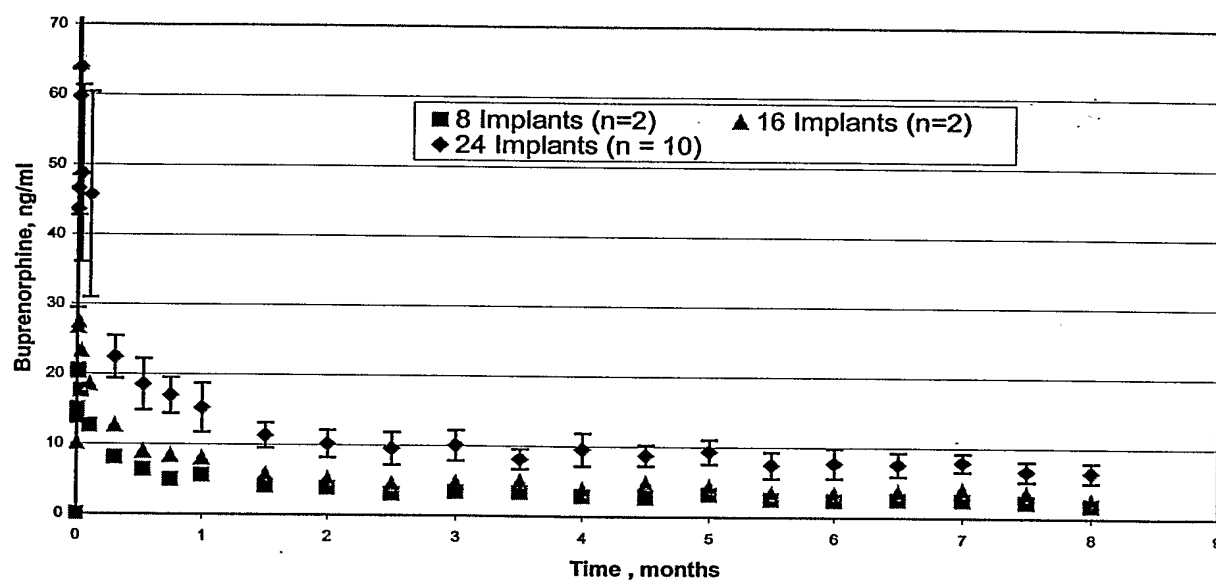
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FIGURE 1**A****B**

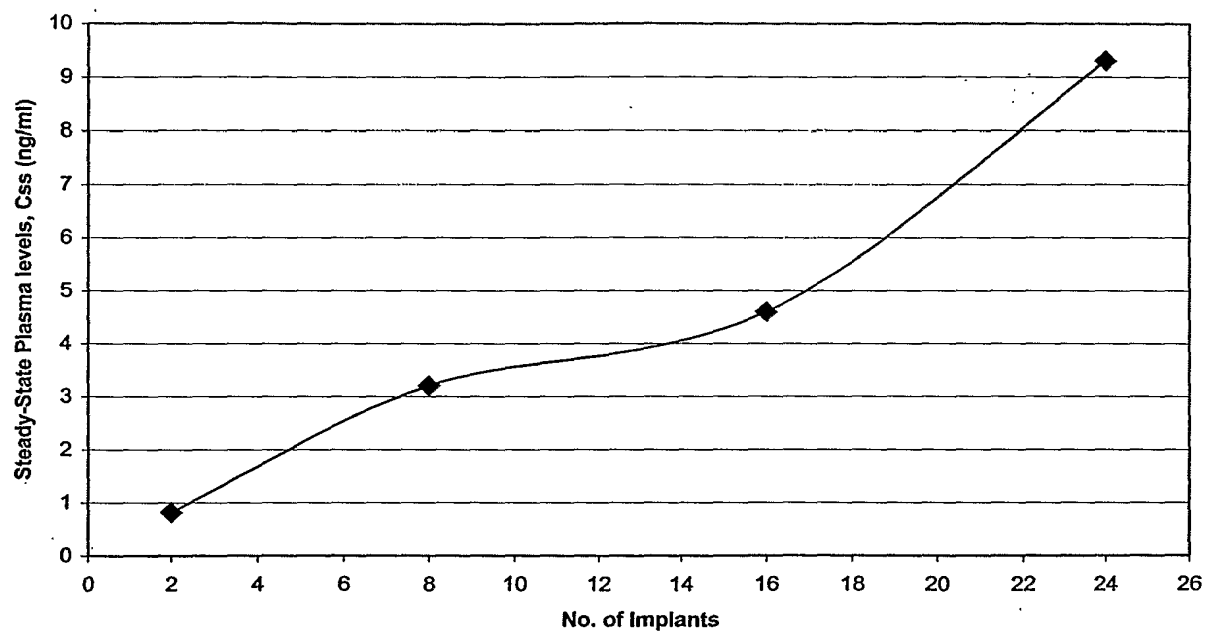
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FIGURE 2

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FIGURE 3

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FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/17401

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 13/00, 2/00; A61K 9/00

US CL : 424/422, 423, 425, 400

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/422, 423, 425, 400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,633,000 A (GROSSMAN et al) 27 May 1997 (27.05.1997), column 2, line 21 through column 4, line 6.	1-6, 12-17
Y	US 5,919,473 A (ELKHOURY) 06 July 1996 (06.07.1996), column 5, line 44 through column 8, line 31.	1-6, 12-17
A	US 5,486,362 A (KITCHELL et al) 23 January 1996 (23.01.1996), column 18, line 60 through column 20, line 14.	1-6, 12-17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

21 July 2003 (21.07.2003)

Date of mailing of the international search report

20 AUG 2003

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

PCT/US03/17401

Continuation of B. FIELDS SEARCHED Item 3:

WEST

opioid, buprenorphine, matrix, implant, ethylene vinyl acetate, subcutaneous

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/17401

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 7-11 and 18-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.